Review Article Compte rendu

Proteinuria in dogs and cats

Leyenda Harley, Cathy Langston

Abstract — Proteinuria is defined as the presence of protein in the urine. Normally, circulating serum proteins are blocked by the glomerulus due to size and/or charge. Any small proteins that pass through a healthy glomerulus are reabsorbed by the renal tubules or broken down by renal tubular epithelial cells. Persistent proteinuria, in the absence of lower urinary tract disease or reproductive tract disease, is usually an indication of renal damage or dysfunction. Less commonly persistent proteinuria can be caused by increased circulating levels of low molecular weight proteins. This article reviews mechanisms of proteinuria in dogs and cats and discusses the importance of screening for and ultimately treating proteinuria.

Résumé — Protéinurie chez les chiens et les chats. La protéinurie se définit comme la présence de protéines dans l'urine. Normalement, les protéines sériques en circulation sont bloquées par les glomérules en raison de la taille et/ou de la charge. Toutes les petites protéines qui circulent dans un glomérule en santé sont réabsorbées par les tubules rénaux ou décomposées par les cellules tubulaires épithéliales. Une protéinurie persistante, en l'absence d'une maladie des voies urinaires inférieures ou d'une maladie de l'appareil de reproduction, est habituellement une indication de dommages ou de troubles rénaux. Une protéinurie persistante moins courante peut être causée par des niveaux accrus de protéines de faible poids moléculaire en circulation. Cet article examine les mécanismes de la protéinurie chez les chiens et les chats et discute de l'importance du dépistage et du traitement subséquent de la protéinurie.

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Why is proteinuria important?

Persistent and increased protein levels in the urine are abnormal. Renal loss of plasma proteins can contribute to hypoalbuminemia; alterations in coagulation factors, cellular immunity, hormonal status, and mineral and electrolyte metabolism; and development of hyperlipidemia in some cases (1–3). Studies over the past decade have shown that proteinuria is highly related to reduced survival in both azotemic and non-azotemic cats and dogs (3–11). In humans, the severity of proteinuria is associated with the rate of progression of chronic kidney disease and is a prognostic indicator in individuals with cardiac disease and diabetic nephropathies (12–15). Reducing proteinuria improves survival in humans and dogs (3,4). Current research is focusing on deciphering the relationship between proteinuria and renal disease and whether or not proteinuria serves merely as a marker for disease or as a contributing factor in renal disease progression.

In humans, a small amount of albumin is normal in the urine (< 0.01 g/L). In cats, what has been deemed significant proteinuria is changing and the International Renal Interest Society (IRIS) now puts feline proteinuria into 3 substages, nonproteinuric [urine potein/creatinine ratio (UP/C) < 0.2], borderline proteinuric (UP/C 0.2 to 0.4), and proteinuric (UP/C > 0.4) (16). In dogs, significant proteinuria is a UP/C > 0.5 with borderline proteinuria 0.2 to 0.5, and non-proteinuric < 0.2. In azotemic dogs, a UPC > 1 is associated with increased risk of uremic crisis and death (4,6).

Physiology, pathophysiology, and mechanism behind proteinuria

Proteinuria results when the normal renal handling of protein malfunctions or is overwhelmed. Normally the small amount of protein that is present in the filtrate is passed through the glomerular capillary wall and reabsorbed by the proximal tubule. The anatomical barrier that is the glomerular capillary wall serves as the primary mechanism by which proteinuria is prevented. Thus, changes in glomerular permeability are what result in the most significant and highest urine protein concentrations.

The glomerular membrane, or glomerular filtration barrier, has 3 layers: the fenestrated endothelium, the glomerular basement membrane, and the podocytes. The podocyte layer has a slit diaphragm between the interdigitating foot processes and it

New Haven Central Hospital for Veterinary Medicine, 843 State Street, New Haven, Connecticut, 06511, USA (Harley); The Animal Medical Center, 510 East 62nd Street, New York, New York 10065, USA (Langston).

Address all correspondence to Dr. Leyenda Harley; e-mail: leyendaharley@hotmail.com

Table 1. Conditions or diseases that may contribute to proteinuria

	Cat	Dog
Pre-renal	Multiple myeloma Systemic hypertension Drug reactions Acute pancreatitis Hyperthyroidism (seizures, heat stroke, fever, extreme exercise, congestive heart failure)[a]	Multiple myeloma Systemic hypertension Drug reactions Acute pancreatitis Hyperadrenocortism (seizures, heat stroke, fever, extreme exercise, congestive heart failure)[a]
Renal	Acute renal failure Chronic renal failure **Glomerulopathy** (see Table 2) Acute pancreatitis Viral disease Drug reactions Systemic hypertension Diabetes mellitus Hyperthyroidism Endocarditis Exogenous steroid use Any severe inflammatory disease, neoplasia, infectious or immune-mediated disease	Acute renal failure Chronic renal failure **Glomerulopathy** (see Table 2) Acute pancreatitis Viral disease Drug reactions Systemic hypertension Diabetes mellitus Hyperadrenocorticism Immune-mediated disease (systemic lupus erythematosis, Immune-mediated hemolytic anemia, polyarthritis, hepatitis) Tick-borne disease Leptospirosis Endocarditis Heartworm disease Exogenous steroid use Any severe inflammatory disease; (IBD, skin, dental), neoplasia, infectious or immune-mediated disease
Post-renal	Lower urinary tract disease Reproductive tract disease	Lower urinary tract disease Reproductive tract disease

[a] Human data. Additional species-specific studies are necessary.

is this layer that is perhaps the most important layer in protecting against proteinuria. Both size and charge selectivity within the podocyte layer prevent excess protein filtration, with very few proteins larger than albumin (69 000 Da) or negatively charged getting through the slit diaphragm (3,17).

The vast majority of proteins that pass through the filtration barrier are taken up through the proximal tubule by endocytosis and subsequently subjected to lysosomal degradation. Because this is a receptor-mediated process, there is a saturation point at which the tubules function at maximum capacity. When all receptors are bound, the remaining proteins in the filtrate pass through into the urine.

Hemodynamic factors affect proteinuria. Afferent and efferent renal arterioles constrict or dilate in response to angiotensin II, local prostaglandins, endothelin, and other vasoactive mediators. Glomerular hypertension results when glomerular capillary pressure rises due to afferent arteriolar tone reduction relative to efferent arteriolar tone. Glomerular hypertension causes proteinuria due to increased single nephron glomerular filtration rate (GFR) enlarging the radii of the pores within the filtration barrier and thus ultrafiltration of proteins occurs (18).

Classification of proteinuria

Traditionally, proteinuria has been classified into 3 categories: pre-renal, renal, and post-renal. Ways to further classify renal proteinuria include physiologic or functional proteinuria *versus* pathologic proteinuria. Pathological proteinuria can further be divided into urinary *versus* non-urinary causes.

Pre-renal proteinuria is a low-level proteinuria caused by an overabundant filtered load of low molecular weight proteins that overwhelm the reabsorptive capacity of the proximal tubule (overload proteinuria). Examples of this include the presence of hemoglobin, myoglobin, and immunoglobulin light-chain monomers and dimers (Bence Jones proteins from neoplastic plasma cells) in the urine.

Renal proteinuria includes all forms of functional and pathologic proteinuria. For renal proteinuria to occur there must be an alteration in renal physiology. In pathologic renal proteinuria the defect is in the glomerular filtration barrier, in tubular reabsorption, or with interstitial damage. Pathologic renal proteinuria is often the most persistent cause of proteinuria and the highest levels of protein in the urine are usually secondary to glomerular disease (alterations in the glomerular filtration barrier). Pathologic glomerular disease (such as in glomerulonephritis and amyloidosis) often results in a UP/C $>$ 2.0 in dogs and cats but can occur with even smaller ratios (2,4,19). Defects in tubular reabsorption of protein can also result in renal proteinuria (such as occurs in Fanconi's syndrome). Glomerular and tubular proteinuria can be differentiated using a sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) testing method (3). For renal interstitial or parenchymal disease to result in proteinuria there must be inflammation

Table 2. Glomerular diseases in dogs and cats[a]

Glomerular disease	Diseases thought to contribute	Breeds shown to be predisposed	
Membranoproliferative glomerulonephritis (MPGN)	Arthropod-borne infections: Lyme borreliosis Babesiosis RMSF Ehrlichiosis Hepatozoonosis Leishmaniasis Viral disease: Canine adenovirus 1 FIP FeLV FIV Leptospirosis[b] Parasitic disease Dirofilariasis Trypanosomiasis Schistosomiasis Chronic bacterial infection Neoplasia	American foxhound (secondary to leishmaniasis) Bernese mountain dog (autosomal recessive) Brittany spaniel (complement deficiency) Doberman pinscher (secondary to sulfa drugs) Labrador retriever, Shetland sheepdog, and golden retriever (associated with *Borrelia burgdorferi*)	
Membranous nephropathy (MN)		Doberman pinscher	
Mesangial proliferative glomerulonephritis (PGN)	Gastrointestinal disease Allergies Systemic lupus erythematosis Post-bacterial infections	Soft-coated wheaten terrier (SCWT)	
Amyloidosis		Beagle Collie English foxhound Walker hound	Familial in: Shar pei Abyssinian cat Siamese cat
Glomerulosclerosis	Hypertension Steroid use Hyperadrenocortism Increasing age	Newfoundland	
Minimal change disease (MCD)	Ehrlichiosis Drug reactions	German shepherd (secondary to *Ehrlichia canis*)	
Focal segmental glomerulosclerosis (FSGS)		Bullmastiff SCWT	
Alport's-like syndrome (hereditary nephritis including X-linked nephritis)		Bull terrier Dalmatian Samoyed	
Other hereditary glomerulopathy or nephropathy (primary glomerulopathy)		Basenji Beagle Boxer English cocker spaniel Doberman pinscher Greyhound (associated with vasculitis and skin lesions)	Norwegian elkhound Pembroke Welsh corgi Rottweiler Samoyed
Juvenile renal disease (renal dysplasia)		Alaskan malamute Beagle Bernese mountain dog Border terrier Boxer Bull mastiff Cairn terrier Cocker spaniel Dalmatian Doberman Dogue de Bordeaux Dutch kookier Finnish harrier Golden retriever	Gordon setter Irish wolfhound Lhasa Apso Miniature schnauzer Newfoundland Pembroke Welsh corgi Rhodesian ridgeback Rottweiller Samoyed Shih tzu SCWT Standard poodle Weimaraner

[a] Data from: Littman, MP. Protein-losing nephropathy in small animals. Vet Clin Small Anim 2011;41:31–62.
[b] Proteinuria associated with leptospirosis is often caused by tubular damage or vasculitis. MPGN has been associated with leptospirosis although it may be attributable to co-infections (i.e., heartworm disease) (3).
RMSF — Rocky Mountain spotted fever, FIP — feline infectious peritonitis, FeLV — feline leukemia virus, FIV — feline immunodeficiency virus.

such as in pyelonephritis, leptospirosis, renal neoplasia, and nephroliths.

Functional renal proteinuria (also called physiologic) is characterized by transient, mild proteinuria, and may be caused by heat, stress, seizure, venous congestion, fever, and extreme exercise (19). In dogs and cats, there are minimal studies on causes of functional proteinuria, but swimming has been shown to cause proteinuria in some dogs and may be correlated to stress, more than exercise (20). Dogs confined to cages have higher urinary protein loss compared to dogs with normal activity, perhaps also due to stress (19). Functional proteinuria is never persistent once the underlying condition resolves.

Post-renal proteinuria is due to protein that is deposited in the urine from any part of the urinary tract distal to the kidney. Urinary tract infections, inflammation, and hemorrhage are all examples of this. Genital infections or inflammation (vaginitis, prostatitis) are also post-renal causes of proteinuria and fit into the category of extraurinary post-renal proteinuria. Extraurinary post-renal proteinuria can be minimized by performing cystocentesis. Although there is protein present in red and white blood cells, large quantities need to be in the urine in order for significant proteinuria to occur, thus small amounts of blood contamination from a cystocentesis should not cause significant proteinuria (21). Post-renal proteinuria is never persistent once the underlying condition is removed.

What patient population should be screened for proteinuria?

It isn't just animals with kidney disease that should be screened for proteinuria. Any animal suspected to have 1 or more of the diseases listed in Table 1 or having a breed predisposition for protein-losing nephropathy (PLN) (Table 2) should be screened for proteinuria. Additionally, any dog that tests positive for Lyme disease should be screened for proteinuria based on newer research suggesting the existence of Lyme disease associated glomerulonephritis (3,22,23). As a general rule, a urinalysis that includes an initial semi-quantitative evaluation of proteinuria should be performed on every dog or cat presented for clinical evaluation in which routine blood work is indicated. Detection of proteinuria should prompt a diligent search for any underlying disease that may be contributing. If proteinuria is persistent and/or does not resolve after treatment of the underlying disease then further steps to monitor, treat, or pursue additional diagnostics are indicated.

Testing for proteinuria

Proteinuria seen on 3 serial urine tests $\geq$ 2 wk apart with benign/normal sediments (except for hyaline casts which are themselves a consequence of proteinuria) should make you highly suspicious of pathologic renal proteinuria. When proteinuria is detected it is the job of the clinician to determine the origin.

Comparing diagnostic tests for proteinuria

Albumin is the predominant protein present in most cases of proteinuria and most commercial tests for proteinuria detect albumin. Proteinuria exists when albumin in the urine is in excess of 0.30 g/L. Data on urinary albumin concentration and urinary total protein concentration are similar and there is no advantage of one over the other. The following tests should be used to complement one another.

Traditional reagent pad "Dipstick" colorimetric method. This test is most sensitive for albumin but can detect other proteins. This is often the first screening test used to detect albumin. This is a sensitive test, but the results can be falsely elevated with highly concentrated urine or pigmented urine (although the false positive is often no greater than a reading of trace or 1+) since the sticks were designed for human urine which is rarely as concentrated as dog or cat urine. Acidic urine can cause false negative results while alkaline urine can cause false positive results (19). If **any** protein is detected on a dipstick, more quantitative assessment of proteinuria is warranted. Performing the sulfosalicylic acid (SSA) test can help delineate between a true and a false positive dipstick test on a concentrated urine sample. A negative dipstick reading in a dog is a reliable indicator of absence of proteinuria, but false negative results are possible with cats (19).

Sulfosalicylic acid (SSA) turbidimetric method. Some laboratories perform this test automatically whenever a dipstick reading is trace or greater. This is a semi-quantitative test for protein and is simple but subject to operator error. The test is performed by using equal parts urine supernatant to 5% SSA in a glass tube and grading protein precipitation based on turbidity. False positive results may occur if the urine contains radiographic contrast agents, cephalosporins, penicillin, thymol, or sulfisoxazole (19). There are fewer false negatives as the SSA test can detect protein at $>$ 0.05 g/L and can detect Bence Jones proteins and globulins (19). A positive SSA test should be followed up with a UP/C determination.

Urine protein: creatinine ratio (UP/C). The UP/C has become the gold standard test for proteinuria and should be run on any patient testing trace or greater on a urine dipstick or positive on SSA. Ideally, protein is measured over a 24-hour period (collection of all urine produced in 24 h) but this is impractical in animals. The urine protein to creatinine ratio, performed on a single random urine sample, has a close correlation to the 24-hour urine protein quantification (24,25).

Microalbuminuria. The lower limit of urine protein detection by dipstick colorimetric tests is approximately 0.30 g/L. The concentration of albumin suspected to be normal in dogs and cats is $<$ 0.01 g/L. Microalbuminuria is defined as an albumin concentration $\geq$ 0.01 and $<$ 0.30 g/L. The significance of early increases in albuminuria (microalbuminuria, MA) is not known in dogs and cats but may indicate glomerular damage undetectable by other methods. In humans it is a predictor of progression of diabetic nephropathy. Microalbuminuria is elevated in dogs and cats with various underlying diseases (not just kidney disease) and may serve as an early screening test for subclinical disease in general, especially hereditary nephropathies (3,26,27). One study suggests that urinary albumin may increase with age in healthy cats (20). Caution must be used when interpreting the significance of MA as a predictor of early renal disease in cats as the human and dog studies of MA in kidney

disease focus on glomerular disease, something that is clinically not as prevalent in cats.

There are several species-specific antibody mediated methods of assessing microalbumin levels in the urine. The early renal damage (ERD) Health Screen™ by Heska consists of canine and feline specific semi-quantitative tests based on subjective interpretation of a color change. Studies have shown that there is not always a correlation between MA and UP/C in cats. The UP/C ratio can be elevated without an increase in MA (28). There are repeatability issues with the semi-quantitative test and thus it should never be relied on as the sole test for proteinuria and is not a recommended test by the authors. Quantitative MA tests are offered by many commercial laboratories.

Microalbuminuria testing should be considered in animals that are predisposed to or suspected to have renal disease, hypertension, and/or systemic conditions frequently complicated by proteinuria that test negative for proteinuria by other methods, or as an early screening tool for hereditary nephropathies.

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). SDS-PAGE is used to distinguish between glomerular versus tubular proteinuria once pre-renal and post-renal causes have been ruled out by using gel electrophoresis to differentiate the sizes of proteins in the urine. Larger proteins ($>$ 69 000 Da) are associated with glomerular disease and smaller proteins with tubular disease (3). This test is not commercially available.

Is proteinuria a consequence of or a contribution to renal injury or both?

There is no established cause and effect relationship between proteinuria and the progression or development of renal failure in animals. Proteinuria is associated with reduced survival, but we don't know whether the proteinuria is the marker or the cause. Glomerular hypertension, which enhances proteinuria, may be the cause of the increased mortality and has been proposed as a factor that contrbutes to chronic kidney disease (2). Studies in humans suggest that proteinuria may be a cause rather than a consequence of renal injury. Tubular and interstitial injury occurs in patients with proteinuria and it is suspected that proteinuria contributes to the progression of renal damage by invoking interstitial inflammation and fibrosis around renal tubules (29,30). Filtered proteins may directly damage tubular cells or may activate complement and chemoattractants leading to the formation of inflammatory mediators such as transforming growth factor beta, platelet-derived growth factor and endothelin-1, which contribute to fibrosis. Renal genes responsible for the synthesis of vasoactive and proinflammatory molecules are upregulated when proteinuria is present (2,31). Although the cause and effect relationship is controversial, many authors feel that proteinuria coupled with ongoing renal injury are manifestations and markers of an underlying yet undefined aggressive pathophysiologic process.

Is proteinuric renal disease worse than other forms of renal disease?

Animals with any form of kidney disease that also have proteinuria (cats with UP/C $>$ 0.4 and dogs with UP/C $>$ 0.5) have a worse prognosis and shorter long-term survival than non-proteinuric animals with kidney disease (3,7,32). Most forms of proteinuric renal disease, however, are glomerular diseases. What is important to note is that proteinuric renal disease is, by definition, renal proteinuria with or *without* azotemia. Thus an animal does not have to have an elevated blood urea nitrogen (BUN) or creatinine to have renal damage.

Most of the time renal proteinuria is due to glomerular dysfunction, especially when it is present in the absence of azotemia. Alterations in glomerular permeability occur as a result of glomerular hypertension, endothelial cell dysfunction, or primary glomerular disease (amyloidosis, glomerulonephritis, hereditary glomerulonephropathies) (3). Glomerular disease can be due to immunological or non-immunological causes (3). In humans, hundreds of genetic mutations causing problems with the slit diaphragm or glomerular basement membrane have been described (3). Table 2 illustrates the most common forms of glomerular disease in dogs and cats.

Primary glomerular disease is much more common in dogs than in cats (3). The most significant clinicopathologic sign suggestive of glomerular disease in dogs is severe proteinuria (UP/C $>$ 2). Other findings that may be present include hypoalbuminemia, hypercholesterolemia, hypertension, ascites, or peripheral edema and pleural effusion (3,5). Azotemia is not always present initially. In the dog, amyloidosis accounted for 23% of glomerular disease in 1 study and beagles, collies, Walker hounds, and English foxhounds were at increased risk (5). Acquired or reactive glomerular amyloidosis results in very high proteinuria (UP/C $>$ 10) (2,3,5). Familial amyloidosis of the Chinese shar pei is different, often resulting in renal medulla amyloid deposition and thus proteinuria can be absent in some dogs (2,3). In the cat, glomerular disease is much less common but can have a presentation similar to that of dogs. Diseases that can cause significant proteinuria in the cat include feline infectious peritonitis (FIP), toxoplasmosis, feline leukemia virus (FeLV) infection, feline immunodeficiency virus (FIV) infection, chronic immune stimulating diseases, and neoplasia. Abyssinian and Siamese cats are predisposed to amyloidosis (3). Most chronic kidney diseases in the cat, however, are characterized by chronic tubulointerstitial damage with the absence of proteinuria (32). In cats, the degree of proteinuria is inversely related to survival, with a median survival time of 281 d in cats with chronic kidney disease (CKD) with UP/C $>$ 0.4 compared to 766 d when the UP/C was $<$ 0.4 (7).

When is it time to intervene? What are the goals of treatment?

If *borderline* proteinuria is detected, animals should be re-evaluated in 2 to 4 mo. If proteinuria (UP/C $>$ 0.4 in a cat and $>$ 0.5 in a dog) is repeatable on 2 or more serial urine tests with benign (inactive) sediments, then a workup is warranted (4). Minimum diagnostic database including complete blood (cell) count (CBC), chemistry panel, urine culture, and blood pressure should be performed. Taking these results into consideration, the physical examination and history should also play a role in guiding the next step in diagnostics. In dogs, tick-borne disease titers, heartworm test, abdominal ultrasound, and testing for hyperadrenocortism should be considered dependent

Table 3. Anti-proteinuric drugs

	Feline dose	Canine dose
ACE inhibitors		
— Enalapril[a]	0.25 to 0.5 mg/kg body weight (BW), PO, q12 to 24h	0.5 mg/kg BW, PO, q12 to 24h
— Benazapril[a]	0.25 to 0.5 mg/kg BW, PO, q12 to 24h	0.25 mg/kg BW, PO, q12h
— Lisinopril[a]	0.25 to 0.5 mg/kg BW, PO, q12 to 24h	0.25 to 0.5 mg/kg BW, PO, q12 to 24h
Angiotensin II receptor antagonists		
— Losartan[b]	No data	0.5 to 1 mg/kg BW/d
— Telmisartan[b]		
Aldosterone receptor antagonist		
— Spironolactone[a]	0.5 to 1 mg/kg BW/d	0.5 to 1 mg/kg BW/day
Omega 3 Fish Oil[b]	Minimum of 1 g/4.55 kg BW, q24h	Minimum of 1 g/4.55 kg BW, q24h
Antihypertensive drugs (if animal persistently hypertensive despite ACE inhibitor): e.g., Amlodipine[a]	0.2 to 0.4 mg/kg BW, q12h	0.2 to 0.4 mg/kg BW, q12h

[a] Plumb DC. Veterinary Drug Handbook, 7th ed. Ames, Iowa: Wiley-Blackwell, 2011.
[b] No published dose in dogs and cats. Dose extrapolated from human data and suggested dose based on authors' experience.

on location, history, and physical examination. Leptospirosis titers should also be considered in dogs with acute proteinuria, especially if they have polyuria and polydypsia (3,33). In cats, thyroxin measurement (if over age 4) and FeLV and FIV screening should be part of the initial testing. Additional testing such as feline pancreatic lipase level, or imaging should be dependent on history and physical examination. Looking for and treating underlying systemic disease such as infection, neoplasia, inflammatory disease, and immune-mediated disease is recommended in both dogs and cats. If treatment of concurrent disease does not result in reduction of proteinuria, or if an underlying disease cannot be detected then additional treatment is needed if UP/C values are greater than 2.0 in nonazotemic cats and dogs or greater than 0.4–0.5 in azotemic cats and dogs, respectively (3,16,19). The goal of treatment should be to achieve the lowest level of proteinuria possible: ideally > 50% reduction in proteinuria in the dog and greater than 90% reduction in the cat (2–4,19).

Renal biopsy

If renal proteinuria is persistent and an underlying cause cannot be found, a renal biopsy should be considered. Performing a renal biopsy in patients with chronic renal failure is not likely to be as useful and is unlikely to alter prognosis and treatment plan or outcome. For acute protein-losing nephropathies, prognostic information and targeting of therapy can be gained from a properly performed and properly processed renal cortical biopsy, whether it is obtained by ultrasound guidance or surgery. Renal biopsies are not without risk, however, and patients must be carefully selected because of the risk. There is a nearly 10% chance of bleeding to the point of needing a blood transfusion in dogs and 17% in cats (34). Mortality associated with renal biopsies in dogs and cats is estimated at 3%. Several factors increase the risk, including anemia, severe azotemia, and a small-sized patient. Biopsies should always be taken of the cortex; the medulla should be avoided.

Electron microscopy (EM), immunofluorescent antibody (IFA) and special staining should be performed on all renal biopsies in addition to routine hematoxylin & eosin (H & E) staining. Electron microscopy is necessary to detect immune deposits and to detect basement membrane or podocyte abnormalities. Immunofluorescent antibody helps characterize any immune deposits that are present. Individuals wishing to perform a renal biopsy are encouraged to contact a specialist and obtain a "renal biopsy kit" which includes special media and instructions on where and how to submit the biopsy. Detailed information regarding the indication and value of a renal biopsy and the pathology and genetics of renal lesions are reviewed elsewhere (3).

Treatment should be aimed at reducing proteinuria to the lowest possible level

Any infectious, inflammatory, metabolic, or neoplastic underlying condition that may be present should be treated. Blood pressure should be evaluated and hypertension should be treated if present. Initial follow-up should be in 1 to 4 wk for blood pressure, physical examination, ultrasound, UP/C, and serum albumin and creatinine when making changes in therapeutic plan and every 3 to 6 mo for stable patients. The goal is to achieve a > 90% reduction in proteinuria in cats and > 50% reduction in dogs.

Diet. Moderately protein-restricted diets offer a way to reduce the overall renal trafficking of protein. If circulating protein can be lowered then there is less risk of protein overload across the filtration barrier and less tubular protein reabsorption. Diet has a large effect on the magnitude of proteinuria (3,35). Too severe restriction of protein intake can lead to loss of body weight and decreased plasma protein concentration. Commercial renal diets for dogs and cats are moderately restricted in protein content and contain restricted amounts of sodium. Samoyeds with hereditary nephritis lived 53% longer when fed a protein, lipid, calcium, and phosphorus restricted diet (3). The effect of diet on the magnitude of proteinuria and rate of disease progression has yet to be evaluated by controlled trials in dogs or cats with proteinuric nephropathies. Diet alone is suspected to be inadequate in treating animals suffering from glomerular disease.

Angiotensin converting enzyme (ACE) inhibitors have been shown in humans and in experimental animal models to reduce proteinuria and slow the progression of renal injury in proteinuric subjects (4). This benefit is independent of the effect these inhibitors have on systemic blood pressure. Benazepril is an ACE inhibitor licensed for use in cats in Europe and Japan and is indicated in the treatment of chronic renal failure in cats. It reduces glomerular capillary pressure both experimentally and clinically in cats (8,18,36). Although studies in cats have shown reductions in proteinuria with the use of ACE inhibitors they have not demonstrated a clear benefit in terms of survival or reduced likelihood of developing azotemia. This is contrary to studies in dogs and humans, which have shown a decreased risk in progressive azotemia and increased survival (4,18). There is no benefit of using benazepril over enalapril in either dogs or cats other than that benazepril can often be dosed once daily (Table 3) (3). Angiotensin coverting enzyme inhibitors are contraindicated in animals that are dehydrated until hypovolemia can be corrected.

Angiotensin II receptor antagonists (ATRA). Losartan is the most commonly used angiotensin II receptor blocker in small animals; however, no data exist on its use in dogs or cats. Table 3 outlines dosing of ATRAs. In humans, ATRAs are renoprotective and reduce proteinuria when used alone or in conjunction with ACE inhibitors (37). The ATRAs work on alternate pathways in the production of angiotensin II and are synergistic with ACE inhibitors (38).

Aldosterone antagonists. Newer research in humans has shown that the mineralocorticoid antagonist spironolactone at relatively low doses reduced proteinuria up to 34% and had a greater effect than ATRAs (39). There are no data on its use in dogs or cats for this purpose but spironolactone is relatively well-tolerated in animals and should be considered for animals not responding to ACE inhibitors or animals with existing hypertension. It can be used solely or in conjunction with ACE inhibitors (see Table 3 for dosing). Blood pressure and potassium levels should be monitored and it is contraindicated in animals with low blood pressure or hyperkalemia.

Omega 3 (eicosapentenoic acid) supplementation. High dose omega 3 polyunsaturated fatty acids (n3 PUFAs) in the form of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to reduce proteinuria in humans with glomerular disease (40). It is also possible that renal eicosanoid production may be affected, reducing inflammation and vasoconstriction; the n3 PUFAs are renoprotective in the dog (2,3,41). Dogs consuming n3 PUFAs have lower mortality, increased renal function, and reduced proteinuria and cholesterol (2,32,41). The dose of n3 PUFAs is not known in dogs and cats and dosing is extrapolated from human data (Table 3). Prescription renal diets, however, are often supplemented with n3 PUFAs (19).

Immunosuppressant therapy. Immunosuppressants should be reserved for use when a diagnosis of immune-mediated glomerulonephritis has been made via a renal biopsy. No blinded studies exist, but published protocols using intravenous cyclophosphamide and methylprednisolone sodium succinate (Solu-Medrol) or intravenous Solu-Medrol and oral azathioprine or intravenous Solu-Medrol and mycophenolate combination therapy have been used in dogs with immune-mediated glomerulonephritis (IMGM) (3). These protocols as well as chlorambucil and cyclosporine have all been used in dogs with suspected Lyme nephritis. A lack of controlled trials evaluating efficacy and safety of these drugs in treating protein-losing nephropathies limits recommendations. In fact, using steroids without evidence to do so could potentially worsen renal disease by increasing proteinuria, and the risk of thromboembolism, hypertension, glomerulosclerosis, and gastric ulceration (3). In humans, response to immunosuppression depends on the specific type of glomerular disease. Minimal change disease (MCD), IgA nephropathy and most forms of IMGN tend to be steroid responsive. Membranous nephropathy (MN), IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), and lupus have been treated with pulse or alternate day steroids and alkylating agents. Cyclosporine can help in some cases of MN. Most genetics-related protein losing nephropathies in humans, glomerulosclerosis and focal segmental glomerulosclerosis (FSGS) are refractory to steroids and are treated supportively (3,42). Other diseases are progressive despite all therapy.

Anticoagulants. Low dose acetylsalicylic acid (aspirin) should be considered as an adjunct therapy for protein losing nephropathies, given that antithrombin III (AT) is often lost into the urine making animals hypercoagulable. Additionally, aspirin may reduce fibrin deposits within the glomerulus and thus may be helpful in reducing disease progression. As a general rule to help guide therapy, dogs with AT level $< 70\%$ and/or with fibrinogen level > 8.8 μmol/L should be treated (19). Others recommend treatment in all cases with hypoalbuminemia since animals with serum albumin levels < 25 g/L are more likely to have AT loss (3). Ongoing research on the use of thromboelastography (TEG) as a measure of hypercoagulability in patients with PLN shows that dogs with PLN may be hypercoagulable independent of AT or albumin level (43,44). The dose of aspirin recommended is 0.5 to 1.0 mg/kg body weight/d in dogs and 5 mg every 72 h in cats (3). Heparin is not useful as it binds to AT.

Conclusion

Increase in urinary protein excretion correlates with decrease in survival and this is independent of any other factor. Proteinuric renal disease progresses more rapidly than nonproteinuric renal disease and reduction in urinary protein excretion slows progression of renal disease and renal interstitial inflammation in humans and dogs. Thus it is speculated that proteinuria itself contributes to ongoing renal damage. If proteinuria is present and persistent then efforts should be made to diagnose the cause and reduce the level. UP/C values > 0.5 in the dog and > 0.4 in the cat are significant; values > 0.2 in the cat and dog are borderline and warrant investigation. The clinician should try to rule in or rule out pre-renal or post-renal causes of proteinuria by looking for and treating any underlying diseases. If renal proteinuria is persistent and significant, therapy should be targeted at reducing proteinuria to the lowest achievable level. Renal biopsy is a useful tool to aid in diagnosing the underlying cause of severe renal proteinuria and the results help

in determining prognosis and guiding therapy. Renal biopsies should be considered in select patient populations suspected of having glomerulonephritis.

It is likely that immunosuppressant therapy will play an important role in the management of Lyme nephritis and other protein losing nephropathies in veterinary medicine in the future. In humans, categorizing and treating proteinuric and glomerular renal disease is more advanced and further studies are needed in dogs and cats. Controlled trials evaluating efficacy and safety of immunosuppressant drugs in dogs with a biopsy diagnosis of immune mediated glomerulonephritis will improve how veterinarians approach protein-losing nephropathies. CVJ

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